ORIGINAL RESEARCH

Overview of Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Patients with Type 2 Diabetes

Kelvin Lingjet Tran, DO; Young In Park, DO; Shalin Pandya, DO; Navin John Muliyil, DO; Brandon David Jensen, DO; Kovin Huynh, DO; Quang T. Nguyen, DO, FACP, FACE, FTOS

BACKGROUND: It is estimated that 29.1 million people or 9.3% of the US population have diabetes, which contributes to considerable medical and financial burden. Type 2 diabetes mellitus is characterized by insulin resistance and insulin secretion impairment leading to hyperglycemia. The presence of insulin resistance is strongly correlated with obesity.

OBJECTIVE: This article reviews the available glucagon-like peptide-1 (GLP-1) receptor agonists and their role in the management of patients with diabetes, to help guide the selection of the most suitable agent for the individualized treatment of patients with type 2 diabetes.

DISCUSSION: This article reviews the evidence from phase 3 clinical trials for each of the 5 GLP-1 receptor agonists by comparing them against one another and with other existing therapies, including metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas. Incretin-based therapies have emerged as attractive agents for the treatment of type 2 diabetes. They target the GLP-1 hormone, which is partly responsible for insulin release and for attenuating hyperglycemia during meals (ie, the incretin effect). The 2 classes of incretin-based therapy currently available are GLP-1 receptor agonists and DPP-4 inhibitors, which prevent the breakdown of GLP-1. Both classes are attractive options, given their glucose-lowering effects without the adverse effects of hypoglycemia and weight gain. The different mechanisms of action of these therapies result in generally greater efficacy with GLP-1 receptor agonists, albeit at the expense of slightly increased gastrointestinal symptoms. These agents exert their effects by improving glucose-dependent insulin release, suppressing glucagon release, suppressing hepatic glucose output, and decreasing the rate of gastric emptying, thereby reducing appetite. Currently, 5 GLP-1 receptor agonists are available, including exenatide, liraglutide, albiglutide, dulaglutide, and lixisenatide; semaglutide may soon become available as the newest agent. With the exception of the investigational oral semaglutide, which has shown promising results, the other 5 agents are administered as subcutaneous injections, at different dosing intervals.

CONCLUSION: Currently, 5 GLP-1 receptor agonists are available for use in the United States. Although they are all in the same drug class, some significant differences exist among the various GLP-1 receptor agonists. The choice of a specific GLP-1 receptor agonist will depend on the patient preferences, potential adverse effects, and cost.

Stakeholder Perspective, page 187

Am Health Drug Benefits. 2017;10(4):178-188
www.AHDBonline.com

Manuscript received April 3, 2017
Accepted in final form April 21, 2017

Disclosures are at end of text

KEY WORDS: albiglutide, diabetes, DPP-4 inhibitors, dulaglutide, exenatide, GLP-1 receptor agonists, incretin-based therapy, insulin, liraglutide, lixisenatide, metformin, semaglutide, sulfonylureas, type 2 diabetes

It is estimated that 29.1 million people or 9.3% of the US population have diabetes, which contributes to considerable medical and financial burden.[1] Type 2 diabetes mellitus is characterized by insulin resistance, and by some impairment in insulin secretion leading to hyperglycemia. The presence of insulin resistance is strongly correlated with obesity.[1]

A significant challenge in the treatment of diabetes is avoiding the development of hypoglycemia, particularly with sulfonylureas and insulin. Complications of hypoglycemia include unconsciousness, brain damage, and even death if untreated.[1] Another adverse effect associated with the treatment of diabetes is weight gain, which occurs with most antidiabetes agents, including sulfonyl-

Dr Tran, Dr Park, Dr Pandya, Dr Muliyil, Dr Jensen, and Dr Huynh are Residents, Department of Internal Medicine, Valley Hospital Medical Center, Las Vegas, NV; Dr Nguyen is Medical Director, Las Vegas Endocrinology, Clinical Associate Professor, Clinical Education, AZCOM, and Adjunct Associate Professor of Endocrinology, Touro University Nevada.

urea, insulin, and thiazolidinediones.[2] Because obesity is closely linked to diabetes, these agents' efficacy in treating diabetes become partly limited because of their link to weight gain.[2]

Cost is also an important consideration when selecting among the many antidiabetes medications. **Table 1** compares the costs of diabetic agents. Glucagon-like peptide (GLP)-1 receptor agonists are generally the most expensive agents. Of note, the cost of Soliqua 100/33 (insulin glargine and lixisenatide injection), which is a combination of insulin glargine and a GLP-1 receptor agonist, is comparable to other GLP-1 receptor agonists that are given as monotherapy. The cost of individual antidiabetes agents may vary depending on insurance coverage, although coupons are often available for a significant cost reduction. Although the cost of diabetes medications (and associated supplies) is significant (12% of the overall cost of treating diagnosed diabetes), the costs of treating the complications of diabetes (18%) and of diabetes-related inpatient care (43%) are even greater.[3] Therefore, it is more cost-effective for patients when their diabetes is appropriately controlled with medications, as necessary.

The Rationale for GLP-1 Receptor Agonists

The pathology of type 2 diabetes involves inherited traits and environmental factors. The vast majority of patients with type 2 diabetes have a genetic risk for insulin resistance; however, the risk for diabetes also worsens with increasing age and weight.[2] Obese patients have more adipocytes, which release leptin, adiponectin, tumor necrosis factor–alpha, and resistin, and these hormones are thought to further contribute to insulin resistance.

During periods of hyperglycemia, there is an increase in glucose transport into beta-cells of the pancreas, which leads to insulin secretion. It is well-recognized that continued poor control of hyperglycemia leads to a decline in beta-cell function, which is likely a result of decreased insulin gene expression and decreased production of insulin. Therefore, it is important that lifestyle changes and treatments are implemented to maintain euglycemia. Uncontrolled diabetes will eventually lead to complications, such as microvascular disease (ie, retinopathy, nephropathy, and neuropathy), and cardiovascular (CV) events and hypertension.

Insulin secretion occurs in 2 phases. The first phase occurs after a meal, manifested as an immediate rise in insulin lasting approximately 10 minutes. This is followed by a second phase, in which insulin is released more slowly for a prolonged period. Patients with type 2 diabetes have markedly reduced first-phase insulin secretion, which likely explains why the majority have persistently elevated postprandial glucose concentrations despite relatively normal fasting glucose levels.[4,5] The beta-cells in the pancreas respond to this by increasing second-phase insulin response.[6] However, prolonged elevation of insulin from persistent hyperglycemia leads to beta-cell toxicity and ultimately contributes to insulin resistance.[7] Interventions that mimic normal first-phase insulin secretion, rather than the second phase, have been correlated with improved glucose tolerance.[8]

GLP-1 is a naturally occurring hormone responsible for the incretin effect. The incretin effect is a response to release more insulin because of high glucose levels after a meal. Studies suggest that patients with type 2 diabetes have an attenuated incretin effect, possibly because of reduced levels of active GLP-1.[9] Evidence shows that GLP-1 regulates the expression of beta-cell genes by inhibiting beta-cell apoptosis, preventing beta-cell glucolipotoxicity, and improving beta-cell function.[10] GLP-1 has been shown to suppress glucagon release and hepatic glucose output.[10] GLP-1 also decreases the rate of gastric

KEY POINTS

- This article reviews the available glucagon-like peptide-1 (GLP-1) receptor agonists and their role in the management of patients with diabetes.
- Clinical trials demonstrate the superiority of GLP-1 receptor agonists to other antidiabetes drugs in HbA_{1c} reduction, blood pressure reduction, and weight loss, without hypoglycemia risk.
- The 5 GLP-1 receptor agonists available include exenatide, liraglutide, albiglutide, dulaglutide, and lixisenatide.
- A new, oral agent, semaglutide, is currently under FDA review and may soon become available as the newest GLP-1 receptor agonist.
- The GLP-1 receptor agonists are valuable options for the treatment of type 2 diabetes as adjunctive therapy or as monotherapy.

Table 1 Costs of Diabetes Medications, by Class

Drug/drug class	Cost of 30-day supply, range, $
Metformin	5-9
Insulin	145-650
Sulfonylureas	9-15
Pioglitazone	12-17
DPP-4 inhibitors	173-397
SGLT-2 inhibitors	432-443
GLP-1 receptor agonists	492-684

DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2.
Source: Cost obtained from GoodRx based on 30-day supply.

Table 2 Phase 3 DURATION Trials with Exenatide ER[16-22]

Trial	Study drug	Exenatide ER outcomes vs comparator drugs
DURATION-1	Exenatide ER 2 mg vs exenatide 10 mcg twice daily	Greater HbA_{1c} reduction: –1.9% vs –1.5% Greater reduction in lipid profile, total cholesterol, triglycerides Better glucose control, body weight reduction, systolic blood pressure reduction Reduced nausea
DURATION-2	Exenatide ER vs pioglitazone vs sitagliptin; all agents taken with metformin	Greater HbA_{1c} reduction w/ exenatide ER: –1.5% vs –0.9% vs –1.2% Greater weight loss: –2.3 kg vs –0.8 kg vs +2.8 kg Less nausea (5% vs 10.8% vs 9.6%) No hypoglycemia w/ exenatide ER
DURATION-3	Exenatide ER vs insulin glargine, titrated to goal <100 mg/dL	Greater HbA_{1c} reduction w/ exenatide ER: –1.5% vs –1.3% 3 × lower hypoglycemia rate w/ exenatide ER
DURATION-4	Exenatide ER vs metformin vs pioglitazone vs sitagliptin; all in treatment-naïve patients	HbA_{1c} reduction: –1.53% vs 1.48% vs 1.63% vs 1.15% Weight loss: –2.0 kg vs –2.0 kg vs +1.5 kg vs –0.8 kg Nausea & diarrhea: 11.3% and 10.9% w/ exenatide ER No major hypoglycemia occurred
DURATION-5	Exenatide ER vs exenatide; this is similar to DURATION-1	At 24 weeks, greater HbA_{1c} reduction: –1.6% vs –0.9% Greater fasting glucose reduction: –35 mg/dL vs –12 mg/dL Similar weight reduction, adverse effects
DURATION-6	Exenatide ER vs liraglutide	Greater HbA_{1c} reduction w/ liraglutide: –1.48% vs –1.28% More patients reached goal w/ liraglutide: 60% vs 53% Greater weight loss w/ liraglutide

ER indicates extended-release; HbA_{1c}, glycated hemoglobin.

emptying and acid secretion, thereby reducing appetite and contributing to weight loss. GLP-1 is degraded by dipeptidyl peptidase (DPP)-4, resulting in a shorter half-life, as shown in patients with type 2 diabetes and in healthy volunteers.[11] This has led to the development of DPP-4 inhibitors, which inhibit the degradation of GLP-1. GLP-1 had been considered a treatment modality, but it has a very short half-life and would require continuous infusions.[11] This has led to the development of GLP-1 receptor agonists, which are structurally similar to the natural hormone to provide beneficial effects but differ structurally to prevent breakdown by DPP-4.

This article reviews the evidence available for current GLP-1 receptor agonists.

Exenatide

Exenatide (Byetta) is a synthetic derivative of exendin-4 (isolated from salivary secretions of the Gila monster lizard) with a 53% amino acid sequence overlap.[12] In 2005, it became the first GLP-1 receptor agonist to receive approval by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes. As an agonist of pancreatic beta-cells and resistance from DPP-4 inactivation, exenatide has a longer duration of action than GLP-1 and more than 1000-fold potency for lowering glucose than GLP-1.[12] Exenatide has been shown to stimulate insulin production in response to blood glucose concentration, inhibit postprandial glucagon release, slow the rate of gastric emptying, slow the rate of nutrient absorption in the bloodstream, and reduce appetite.[12] It is also found to promote the proliferation of beta-cells and islet-cell neogenesis from precursor cells.[12]

Exenatide was first introduced as a twice-daily injection of 5 mcg for 1 month followed by 5 mcg or 10 mcg. Pharmacokinetics demonstrated a plasma level reaching peak concentrations at 2 to 3 hours after administration with levels remaining detectable for 6 hours after administration. Patients with type 2 diabetes who were inadequately controlled with a sulfonylurea and/or metformin were given 0.08-mcg/kg subcutaneous injections of exenatide, which showed significant reductions in postprandial plasma glucose (PPG) and glycated hemoglobin (HbA_{1c}).[12]

Exenatide was studied in the phase 3 clinical trials AMIGO I, II, and III.[12,13] In all 3 trials, the continuation of previous therapy (with metformin alone, sulfonylurea alone, or the combination of both) was compared between the addition of exenatide and placebo. The exenatide treatment group demonstrated a significant reduction in PPG concentrations and HbA_{1c} compared with the placebo group. Nausea was the most common adverse effect, with an increased rate of nausea in the exenatide groups versus the placebo groups. The rates of hypoglycemia in AMIGO I, which included patients who had received metformin, were equal between the exenatide and the placebo groups; however, in the AMIGO III study, which included patients who had received sulfonylurea and metformin combination therapy, patients receiving 10-mg exenatide had increased hypoglycemia (28% vs 13% in the placebo group). No changes in heart rate, blood pressure, and electrocardiograms were noted. The small increase in cortisol levels normalized by day 28.[12,13]

Buse and colleagues compared exenatide 5 µg twice daily for 4 weeks and then 10 µg twice daily thereafter with placebo in patients receiving insulin glargine.[14] Insulin glargine was titrated to achieve a fasting glucose of <100 mg/dL on the basis of the Treat-to-Target Trial algorithm. The study showed an HbA_{1c} reduction of 1.74% with exenatide versus 1.04% with placebo. No significant increase in hypoglycemia or weight gain occurred. Similar to the AMIGO trials, exenatide was associated with more events of nausea (41% vs 8%, respectively) and vomiting (18% vs 4%, respectively) than placebo.[14]

Exenatide ER

A new formulation of exenatide, exenatide extended-release (ER; Bydureon) 2-mg once-weekly injection was approved by the FDA in 2012 as an adjunct therapy or monotherapy in patients with type 2 diabetes.[15] Exenatide ER reaches therapeutic levels after 2 weeks, and after 6 weeks the drug attains a maximum concentration

higher than that attained by a single injection of exenatide 10 mcg.[15] Six weeks after stopping treatment, the serum concentration of exenatide once weekly declines to insignificant levels.

The phase 3 clinical trials of exenatide ER included the DURATION series, and are summarized in **Table 2**.[16-22] DURATION-1 and -5 compared exenatide twice daily versus exenatide ER, showing that exenatide ER had a greater HbA_{1c} reduction and better glucose control compared with the twice-daily formulation. DURATION-2 and -4 compared exenatide ER with other diabetic oral medications, including pioglitazone, sitagliptin, and metformin, which demonstrated comparable efficacy in reducing HbA_{1c} and significantly reducing weight.[16-21]

Exenatide was associated with an increase in gastrointestinal (GI) adverse effects, including nausea, vomiting, and diarrhea,[16-21] as is expected of the GLP-1 class. Nausea was most notable during the first few weeks of therapy and was minimized by gradual dose titration. In DURATION-2 and -4, no significant differences were reported in the rates of hypoglycemia between exenatide ER and metformin, pioglitazone, or sitagliptin.[18,20] DURATION-3 compared exenatide ER with insulin glargine, showing 3 times fewer hypoglycemic events with the GLP-1 inhibitor than in the insulin glargine group.[19]

Mild injection-site pruritus was observed more often with exenatide ER, but it resolved with treatment continuation.[17] Despite concerns for a possible association of exenatide and the other GLP-1 receptor agonists with increased risk for pancreatitis, this was not observed in the DURATION trials.[15]

Liraglutide

Liraglutide (Victoza) is an acylated analog of GLP-1 that has 97% amino acid sequence identity to the endogenous GLP-1 analog. In 2009, it was the second GLP-1 agonist to be approved by the FDA for the treatment of type 2 diabetes. Liraglutide is a long-acting GLP-1 receptor agonist that is administered once daily as a subcutaneous injection in contrast to twice-daily injections of the first exenatide formulation.[23] Liraglutide has been reported to increase beta-cell mass in animal models via increased beta-cell replication and reduced apoptosis.[24] In a study with normal-weight and obese rats, liraglutide was associated with a reduction in food intake, resulting in weight loss of approximately 15%.[25] Preclinical studies showed improvement in first- and second-phase insulin secretion, implying that liraglutide leads to improved biphasic insulin secretion in response to hyperglycemia.[26,27]

The Liraglutide Effect and Action in Diabetes (LEAD) program is comprised of 6 phase 3 clinical trials, which are summarized in **Table 3**.[28-33] Liraglutide, given as adjunct therapy and as monotherapy, was associated with significant reductions in HbA_{1c} levels, blood pressure, fasting plasma glucose (FPG), and PPG levels.[28-33] Liraglutide is superior to insulin glargine and to twice-daily exenatide in HbA_{1c} reduction. Weight loss was similar between the liraglutide and the exenatide groups, but greater weight loss was seen with liraglutide compared with insulin glargine.[28-33]

The LEAD trials showed that the risk for hypoglycemia is low with liraglutide and is significantly lower than with a sulfonylurea or twice-daily exenatide.[28-33] Like exenatide, liraglutide was associated with increased GI side effects, including nausea and vomiting, which were generally mild and transient. A total of 3.4% of the patients receiving liraglutide in the phase 3 trial withdrew because of nausea.[30] In general, the GI adverse effects can be managed by starting at lower doses of liraglutide and then gradually increasing the dose. Liraglutide was

Table 3 Phase 3 LEAD Trials with Liraglutide[28-33]

Trial	Study drug	Liraglutide outcomes vs comparator drugs
LEAD-1	Liraglutide 1.2 mg & 1.8 mg once daily vs rosiglitazone 4 mg once daily; all concurrently taking sulfonylurea	Significant HbA_{1c} reduction w/ liraglutide 1.2 mg & 1.8 mg: 1.1% vs –0.4% w/ rosiglitazone 4 mg Significant decrease in FPG & PPG w/ liraglutide vs rosiglitazone Minor hypoglycemia, <10%; nausea, <11%; vomiting, <5%; diarrhea, <8%
LEAD-2	Liraglutide 1.2 mg & 1.8 mg vs glimepiride 4 mg; all concurrently taking metformin	Noninferior HbA_{1c} reduction in liraglutide groups: mean decrease, –1% Body weight –2.8 kg w/ 1.8-mg liraglutide vs +1.0 kg w/ glimepiride Less hypoglycemic events in liraglutide groups: 3% vs 17% w/ glimepiride Increased nausea in liraglutide groups
LEAD-3	Liraglutide 1.2 mg & 1.8 mg once daily vs glimepiride 8 mg once daily	HbA_{1c} reductions: –0.84% & –1.23% w/ liraglutide 1.2 mg & 1.8 mg vs 0.51% w/ glimepiride 8 mg No major hypoglycemic events Significantly less minor hypoglycemia: 8% & 12% vs 24%
LEAD-4	Liraglutide 1.2 mg & 1.8 mg vs placebo; all concurrently taking metformin and rosiglitazone	HbA_{1c} reduction: –1.5% vs –0.5% Significant FPG and PPG reductions w/ 1.2-mg & 1.8-mg liraglutide Body weight reductions: –1.0 kg & –2.0 kg w/ liraglutide 1.2 mg & 1.8 mg vs +0.6-kg weight gain w/ placebo Systolic BP reductions: –6.7 mm Hg & –5.6 mm Hg w/ liraglutide 1.2 mg & 1.8 mg vs –1.1 mm Hg w/ placebo Minor hypoglycemia: 7.9% & 9% vs 5.1% No major hypoglycemic events
LEAD-5	Liraglutide 1.8 mg vs insulin glargine; all concurrently taking metformin and glimepiride	Significantly greater HbA_{1c} reduction: –1.33% vs –1.09% Significantly greater weight loss w/ liraglutide: –1.39 kg vs +3.43 kg Systolic BP reduction: –4 mm Hg vs +0.5 mm Hg Major & minor hypoglycemia rates: 0.06 & 1.2 vs 0 & 1.3 events/patient annually
LEAD-6	Liraglutide 1.8 mg vs exenatide 10 µg twice daily, all concurrently taking metformin and sulfonylurea	Significant HbA_{1c} reduction: –1.12% vs –0.79% Greater FPG reduction vs exenatide Weight loss: 3.24 kg vs 2.87 kg (difference not significant) Significantly less minor hypoglycemia w/ liraglutide: 25.5% vs 33.6% 2 patients taking exenatide & sulfonylurea had major hypoglycemia Less nausea w/ liraglutide

BP indicates blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; PPG, postprandial glucose.

Table 4 Phase 3 HARMONY Trials with Albiglutide[39-46]

Trial	Study drug	Albiglutide outcomes vs comparator drugs
HARMONY-1	Albiglutide 30 mg vs placebo	HbA_{1c}: –0.8% vs –0.1% Hyperglycemia events: 24.4% vs 47.7% No significant differences in weight change All GI events: 31.3% vs 29.8% Diarrhea: 11.3% vs 8.0% Nausea: 10.7% vs 11.3% Vomiting: 4% vs 4%
HARMONY-2	Albiglutide 30 mg vs albiglutide 50 mg vs placebo	HbA_{1c}: –0.84% vs –1.04% No significant changes in weight w/ 2 albiglutide doses Similar nausea, diarrhea, vomiting, hypoglycemia rate in all groups, including placebo
HARMONY-3	Albiglutide 30 mg vs sitagliptin 100 mg vs glimepiride 2 mg vs placebo; all concurrently taking metformin	HbA_{1c}: –0.9% vs –0.4% vs –0.3% (vs placebo) Weight change: –1.21 kg vs –0.86 kg vs +1.17 kg vs –1.0 kg Hyperglycemia rates: 25.8% vs 36.4% vs 32.7% vs 59.2% Diarrhea: 12.9% vs 8.6% vs 10.9% (vs placebo) Nausea: 10.3% vs 6.2% vs 10.9% (vs placebo)
HARMONY-4	Albiglutide vs insulin glargine titrated to fasting plasma glucose goal of 100 mg/dL	HbA_{1c}: –0.7% vs –0.8% Weight change: –1.0 kg vs +1.5 kg Hypoglycemia: 17.5% vs 27.4%
HARMONY-5	Albiglutide 30 mg titrated up to 50 mg vs pioglitazone 30 mg titrated up to 50 mg; all concurrently taking metformin ± glimepiride 4 mg	HbA_{1c} reduction: –0.87% vs placebo HbA_{1c} +0.25 vs pioglitazone: not meeting noninferiority criteria Hypoglycemia: 14% vs 25% vs 14% Weight change: –0.42 kg vs +4.4 kg vs –0.4 kg
HARMONY-6	Albiglutide 30 mg titrated up to 50 mg vs insulin lispro 3 × daily adjusted per glucose level	HbA_{1c}: –0.82% vs –0.66% Weight change: –7.3 kg vs +0.81 kg Severe hypoglycemia: 0 vs 2 events Nausea: 11.2% vs 1.4% Vomiting: 6.7% vs 1.4% Injection-site reaction: 9.5% vs 5.3%
HARMONY-7	Albiglutide 30 mg titrated up to 50 mg vs liraglutide 0.6 mg titrated up to 1.8 mg; all concurrently taking metformin ± sulfonylurea ± thiazolidinedione	HbA_{1c}: –0.78% vs –0.99% Injection-site reaction: 12.9% vs 5.4% GI adverse effects: 35.9% vs 49%
HARMONY-8	Albiglutide vs sitagliptin with GFR >60 mL/min, GFR 30-59 mL/min, GFR 15-29 mL/min; all ± oral diabetes drugs	HbA_{1c}: –0.83% vs –0.52% Time to hyperglycemic rescue longer w/ albiglutide All adverse events: 51.7% vs 25.2% Diarrhea: 10% vs 6.5% Nausea: 4.8% vs 3.3% Vomiting: 1.6% vs 1.2% Hypoglycemia: 24.1% vs 15.9% (sulfonylurea: 22.5% vs 14.2%; no sulfonylurea: 4% vs 4%) Weight change: –0.79 kg vs –0.19 kg

GFR indicates glomerular filtration rate; GI, gastrointestinal; HbA_{1c}, glycated hemoglobin.

associated with a lower antibody formation than exenatide, likely because of the greater (97%) amino acid sequence identity than human GLP-1.[34] Exenatide has a lower sequence identity than liraglutide, which may explain the incidence of anti-exenatide antibody formation in up to 43% of exenatide-treated patients.[35]

There have been few case reports of liraglutide-associated pancreatitis. Studies in rodents have shown that liraglutide induces C-cell proliferation and medullary thyroid adenomas and carcinomas via GLP-1 receptor agonist activation and calcitonin release, but this pattern was not seen in humans. Follow-up studies have been inconclusive to definitively define a cause-and-effect relationship between liraglutide and pancreatitis, because patients with type 2 diabetes already have a 3-fold increased risk for pancreatitis.[36] In the LEADER trial, liraglutide taken for 3.5 years was associated with a 23% reduction in CV events, a 22% reduction in CV mortality, and a 15% reduction in all-cause mortality.[37]

Albiglutide

Albiglutide (Tanzeum) is a GLP-1 agonist that was approved by the FDA in 2014 as an adjunct treatment for diabetes; it is administered as a weekly injection.[38] Albiglutide has 97% homology to the amino acid sequence of GLP-1. A single amino acid substitution (alanine to glycine) renders albiglutide resistant to DPP-4–mediated protein degradation, resulting in a longer half-life. After subcutaneous injection of a single 30-mg dose, patients with type 2 diabetes achieved mean maximum plasma concentration 3 to 5 days after administration. Plasma concentrations reach steady state within 3 to 5 weeks of repeated once-weekly administrations. Albiglutide is currently available as a 30-mg and a 50-mg once-weekly injection.[38]

Albiglutide was tested in the HARMONY phase 3 clinical trials, which comprised 8 studies (**Table 4**).[39-46] HARMONY-2 demonstrated the superiority of albiglutide monotherapy to diet and exercise in glycemic control.[40] In HARMONY-3, once-weekly albiglutide add-on therapy was noninferior to once-daily sitagliptin and once-daily glimepiride at reducing HbA_{1c} levels in patients inadequately controlled with metformin alone,[41] whereas HARMONY-4 and -6 demonstrated that albiglutide was noninferior to insulin therapy in patients inadequately controlled with oral antidiabetes therapy.[42,44] However, in HARMONY-5, albiglutide was found to be inferior to pioglitazone in HbA_{1c} reduction.[43] HARMONY-8 revealed that albiglutide was superior to sitagliptin in patients with and without renal impairment.[46]

Albiglutide demonstrated greater weight loss in all studies compared with sitagliptin, glimepiride, pioglitazone, and insulin therapy, although more GI adverse effects were reported with albiglutide compared with other agents.[39-46] All trials demonstrated no significant differences in rates of hypoglycemia, except in patients with impaired renal disease who used albiglutide and a sulfonylurea.[39-46]

Dulaglutide

Dulaglutide (Trulicity) is a once-weekly subcutaneously administered GLP-1 receptor agonist approved by the FDA in 2014 as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes.[47] The initial dosage is 0.75 mg administered subcutaneously once weekly, which may be increased to 1.5 mg

once weekly for additional glycemic control. Dulaglutide is comprised of 2 identical GLP-1 analog peptide chains (approximately 90% homologous to native human GLP-1) linked to an immunoglobulin (Ig) G4 heavy chain. The alteration of the GLP-1 analog provides protection against degradation by DPP-4, improved solubility, and reduced immunogenicity. The addition of IgG4 increases the size of the protein, which helps decrease the rate of renal clearance, and the Fc fragment of IgG4 prevents antibody formation to further reduce the potential for immunologic cytotoxicity.[47]

Dulaglutide has been studied in comparison with other antidiabetes agents and with placebo in the phase 3 AWARD trials (**Table 5**).[48-54] These trials demonstrate that once-weekly dosing of 1.5-mg dulaglutide was superior to metformin, insulin glargine, and sitagliptin in reducing HbA_{1c} levels; dosing with dulaglutide 0.75 mg was noninferior to these agents. Patients in these trials experienced greater loss with 1.5-mg and with 0.75-mg dosing of dulaglutide compared with other agents. In patients taking dulaglutide and insulin concomitantly, there was either attenuation of the weight gain or overall weight loss compared with patients receiving placebo.[48-54] In AWARD-6, patients receiving liraglutide 1.8 mg experienced greater weight loss than those receiving dulaglutide 1.5 mg.[53]

Similar to other GLP-1 receptor agonists, the most frequently reported adverse events with dulaglutide were GI in nature, including nausea, vomiting, and diarrhea.[48-54] These events were generally mild to moderate, peaked at 2 weeks, and rapidly declined over the next 4 weeks. The majority of adverse events were reported during the first 2 to 3 days after receiving the initial dose and declined with subsequent doses. Hypoglycemic events were not common in patients taking dulaglutide, and occurred less frequently compared with patients receiving insulin therapy, as was shown in AWARD-2 and -4[49,51]; however, significantly more hypoglycemic events were reported with a sulfonylurea as background therapy compared with placebo as demonstrated in AWARD-8.[48-54]

Given its mechanism of action, dulaglutide was evaluated for pancreatic safety. Throughout the AWARD trials, 4 events were reported in patients taking dulaglutide (3 patients receiving dulaglutide 1.5 mg and 1 receiving the 0.75-mg dose). Laboratory studies of pancreatic amylase and lipase in these trials revealed a mean 14% to 20% increase in amylase and lipase levels in patients receiving dulaglutide; however, these events were not predictive of acute pancreatitis. Given the association of GLP-1 analogs with medullary thyroid carcinoma, thyroid safety was assessed as well. In the AWARD trials, only 1 case of medullary thyroid carcinoma in AWARD-5 was reported, although this case was determined to be preexisting.[52]

Table 5 Phase 3 AWARD Trials with Dulaglutide[48-54]

Trial	Study drug	Dulaglutide outcomes vs comparator drugs
AWARD-1	Dulaglutide 1.5 mg once weekly vs dulaglutide 0.75 mg vs exenatide 10 µg twice daily; all concurrently taking metformin and pioglitazone (26-week study)	HbA_{1c}: –1.51% vs –1.3% vs –0.99% Body weight: –1.3 kg vs +0.2 kg vs –1.07 kg No severe hypoglycemia w/ dulaglutide Very similar rates of nausea, vomiting, & diarrhea with dulaglutide 1.5 mg & exenatide Less adverse effects w/ dulaglutide 0.75 mg
AWARD-2	Dulaglutide 1.5 mg vs dulaglutide 0.75 mg vs insulin glargine; all concurrently taking metformin and glimepiride (52-week study)	HbA_{1c}: –1.08% vs -0.76% vs –0.63% Superiority met w/ dulaglutide 1.5 & noninferiority w/ 0.75-mg dose Hypoglycemia rates lower w/ dulaglutide More nausea and diarrhea w/ dulaglutide than glargine
AWARD-3	Dulaglutide 1.5 mg vs dulaglutide 0.75 mg vs metformin titrated up to 2000 mg/day (26-week study)	HbA_{1c}: –0.78% vs –0.71% vs –0.51% Dulaglutide 1.5 mg & 0.75 mg met superiority w/ HbA_{1c} reduction Similar decreases in weight between all 3 groups Nausea, diarrhea, & vomiting were similar between dulaglutide & metformin
AWARD-4	Dulaglutide 1.5 mg vs dulaglutide 0.75 mg vs insulin glargine; all concurrently receiving prandial insulin lispro (52-week study)	HbA_{1c}: –1.64% vs –1.59% vs –1.41% Noninferiority of dulaglutide 1.5 mg vs glargine w/ HbA_{1c} reduction Weight change: –2.88 kg vs –2.39 kg vs –1.75 kg; significance difference w/ dulaglutide 1.5 mg vs sitagliptin More nausea, diarrhea, & vomiting w/ dulaglutide than glargine
AWARD-5	Dulaglutide 1.5 mg vs dulaglutide 0.75 mg vs sitagliptin 100 mg; all concurrently taking metformin (52-week study)	HbA_{1c}: –1.10% vs –0.87% vs –0.39% Both doses met superiority to sitagliptin More nausea, diarrhea, & vomiting w/ dulaglutide
AWARD-6	Dulaglutide 1.5 mg vs liraglutide 1.8 mg; all concurrently taking metformin (26-week study)	HbA_{1c}: –1.42% vs –1.36%; met noninferiority criteria Greater weight loss w/ liraglutide (–2.9 kg vs –3.61 kg) Nausea: 20% vs 18% Diarrhea: 12% vs 12% Dyspepsia: 8% vs 6% Vomiting: 7% vs 8%
AWARD-8	Dulaglutide 1.5 mg vs placebo; all concurrently taking glimepiride	HbA_{1c} difference: –1.3%; superior to placebo Fasting plasma glucose difference: –33.54 mg/dL; superior to placebo Weight loss was significant from baseline w/ dulaglutide, but between-groups difference not significant Hypoglycemia higher w/ dulaglutide (2.37 vs 0.07 events/participant annually) No severe hypoglycemic events

HbA_{1c} indicates glycated hemoglobin.

Lixisenatide

Lixisenatide (Adlyxin) is a once-daily subcutaneous GLP-1 receptor agonist that was approved by the FDA in July 2016 for the treatment of type 2 diabetes in adults.[55] Lixisenatide is designed as C-terminal modification with 6 lysine residues and deletion of 1 proline, allowing it to withstand physiologic degradation by DPP-4. Lixisenatide is renally excreted, with a half-life of 2 to 4 hours. Despite its short half-life, lixisenatide is intended for once-daily dosing as a result of its strong binding affinity to the GLP-1 receptor. No clinically relevant difference was found in the rate of absorption if lixisenatide is injected into the abdomen, thigh, or arm. In a dose-dependent manner, lixisenatide tested at 5-mcg, 10-mcg, and 20-mcg doses reached peak concentrations

Table 6 Phase 3 GETGOAL Trials with Lixisenatide[56-64]

Trial	Study drug	Lixisenatide outcomes vs comparator drugs
GETGOAL-Mono	Lixisenatide 1-step AM vs 2-step AM vs placebo; 12-week study	HbA_{1c}: –0.66% 1-step vs –0.54% 2-step Achieved HbA_{1c} goal (<7%): 46.5% 1-step vs 52.2% 2-step Decrease in body weight: ~2 kg in both groups Symptomatic hypoglycemia: 1.7% in lixisenatide groups vs 1.6% in placebo groups Significant improvements in HbA_{1c}: 2-hr PPG, FPG vs placebo
GETGOAL-F1	Lixisenatide 1-step AM vs 2-step AM; all concurrently taking metformin; 24-week study	HbA_{1c}: –0.9% vs –0.8% vs –0.4% Improved FPG: –0.5 vs –0.6 vs +0.1 mmol/L Body weight: –2.6 kg vs –2.7 kg vs –1.6 kg Symptomatic hypoglycemia: 1.9% vs 2.5% vs 0.6%
GETGOAL-S	Lixisenatide 2-step AM vs placebo; all concurrently taking sulfonylurea; 24-week study	HbA_{1c}: –1.1% mean significant difference vs placebo Significant 2-hr postprandial glucose & FPG vs placebo Body weight: –1.12 kg vs –1.02 kg GI adverse effects: 52.6% vs 29.4% Symptomatic hypoglycemia: 17.1% vs 9.8% No cases of severe symptomatic hypoglycemia in either group
GETGOAL-L	Lixisenatide 2-step AM vs placebo; all concurrently taking basal insulin	HbA_{1c} reduction: –0.4% difference vs placebo Symptomatic hypoglycemia: 28% vs 22% Severe hypoglycemia: 1.2% vs 0%
GETGOAL-P	Lixisenatide 2-step AM vs placebo; all concurrently taking pioglitazone; 24-week study	HbA_{1c} reduction: –0.56% difference vs placebo Significantly improved FPG: –0.84 mmol/L Small decrease body weight w/ lixisenatide & small but insignificant increase w/ placebo Symptomatic hypoglycemia: 3.4% vs 1.2%; no severe episodes
GETGOAL-X	Lixisenatide 2-step AM vs exenatide 10 mcg twice daily; all concurrently taking metformin; 24-week study	Noninferiority in HbA_{1c} reduction vs exenatide FPG reduction was comparable Weight loss: –2.8 kg vs –3.8 kg Serious adverse events: 2.8% vs 2.2% Significantly reduced symptomatic hypoglycemia: 2.5% vs 7.9% Significantly less nausea events: 24.5% vs 35.1%
GETGOAL-M	Lixisenatide 2-step AM or PM vs placebo; all concurrently taking metformin; 24-week study (similar to GETGOAL-F1)	Significant HbA_{1c} reduction: –0.36% difference vs placebo Significant reduction in 2-hr PPG vs placebo No difference in weight loss Nausea: 16.3% vs 2.6% Symptomatic hypoglycemia: 5.6% vs 2.6% No severe symptomatic hypoglycemia
GETGOAL-Mono JAPAN LTS	Lixisenatide 1-step AM vs 2-step AM; 52-week study with primary end point on safety measures	Nausea: 59% vs 36.4% Symptomatic hypoglycemia: 0% vs 6.1% HbA_{1c}, FPG, body weight reduced from baseline
GETGOAL-L-ASIA	Lixisenatide 2-step AM vs placebo; all concurrently taking basal insulin; 24-week study (similar to GETGOAL-S)	HbA_{1c} reduction: –0.88% vs placebo Significant improvement in 2-hr postprandial glucose Nausea and vomiting: 18.2% vs 1.9% Symptomatic hypoglycemia: 42.9% vs 23.6% No severe hypoglycemia
GETGOAL-M-ASIA	Lixisenatide 2-step AM vs placebo; all concurrently taking metformin + sulfonylurea; 24-week study	HbA_{1c} reduction: –0.57% (significant difference) Superior to placebo in lowering 2-hr postprandial glucose Body weight in lixisenatide group trended to decrease

AM indicates morning administration; FPG, fasting plasma glucose; GI, gastrointestinal; HbA_{1c}, glycated hemoglobin; PM, evening administration; PPG, postprandial plasma glucose.

between 1 and 2 hours.[55] Preclinical trials have also shown that the addition of a GLP-1 receptor agonist to insulin analog–like glargine demonstrated a protective effect on beta-cells, suggesting that the combination of these medications may preserve beta-cell mass in patients with type 2 diabetes.[56] Thus, in November 2016, the FDA approved the combination of lixisenatide with insulin glargine (Soliqua 100/33).

Lixisenatide was studied in the 10 phase 3 GETGOAL clinical trials that assessed its efficacy and safety profile (**Table 6**).[56-64] In these trials, the 20-mcg dose of lixisenatide was selected, because it had demonstrated in previous trials the best efficacy-to-tolerability ratio. The phase 3 studies assessed lixisenatide in a 1-step titration as a 10-mcg dose for 2 weeks, then a 20-mcg dose once-daily subcutaneously, and in a 2-step titration as a 10-mcg dose for 1 week, 15-mcg dose for 1 week, and then as a 20-mcg dose. In all these trials except GETGOAL-M,[64] lixisenatide was administered in the morning. No significant differences were seen in efficacy and adverse events between the 1- and 2-step titration groups.[56-64]

Lixisenatide demonstrated superiority in reducing HbA_{1c}, PPG, and FPG compared with placebo monotherapy or adjunct therapy. In GETGOAL-X, lixisenatide demonstrated noninferiority with HbA_{1c} reduction compared with exenatide 10 mcg twice daily. Weight loss was superior with lixisenatide treatment in all trials, except GETGOAL-M,[64] compared with placebo[56-64]; however, in GETGOAL-X, lixisenatide treatment resulted in an average 2.8-kg weight loss compared with 3.8 kg in the exenatide group.[63]

As with other GLP-1 analogs, there was an increase in GI adverse effects with lixisenatide, including nausea and vomiting, as reported in GETGOAL-F1,[58] GETGOAL-S,[59] GETGOAL-L,[60,62] GETGOAL-P,[61] and GETGOAL-M[64]; however, there were fewer reports of nausea compared with exenatide. In all trials where lixisenatide was not combined with insulin, pioglitazone, or a sulfonylurea, no increase in hypoglycemic events was seen compared with placebo. If combined with these agents, the lixisenatide groups exhibited more hypoglycemic events. Compared with exenatide, fewer hypoglycemic events were reported in the patients receiving lixisenatide.[56-64]

CV outcomes were studied with lixisenatide in the separate phase 3 ELIXA trial.[65] Patients who take lixisenatide do not have any increase in CV adverse effects after an acute coronary syndrome compared with placebo. In addition, no significant CV benefit was seen compared with placebo.[65]

Semaglutide

Semaglutide is an investigational agent that was developed as a once-weekly subcutaneous formulation, as well as the first oral GLP-1 analog formulation. The manufacturer applied for regulatory approval by the FDA of the injectable formulation in December 2016, after the phase 3 clinical trial SUSTAIN-6 showed

promising results, including HbA_{1c} reduction, weight loss, and CV benefit.[66] The oral formulation is still in phase 3 clinical trials.[67]

The SUSTAIN-6 trial showed the weekly subcutaneous formulation of semaglutide to have a significant HbA_{1c} reduction of 0.7% with the 0.5-mg dose, and 1% with the 1-mg dose, compared with placebo.[68] Patients in the 0.5-mg group had a weight loss of 2.9 kg, and the 1-mg group had a 4.3-kg weight loss. Nonfatal myocardial infarction occurred in 2.9% of patients receiving semaglutide versus 3.9% in patients receiving placebo. Nonfatal stroke occurred in 1.6% and 2.7% of the patients, respectively. The rate of death from a CV cause was similar in both groups. The rate of new or worsening nephropathy was lower in the semaglutide group than in the placebo group, although the rate of retinopathy complications was significantly higher with semaglutide.[68]

Perhaps the most exciting development in the GLP-1 class is the oral formulation of semaglutide that has shown promising results in its phase 2 trial and is currently undergoing a phase 3 study.[69] This oral formulation is combined with the absorption enhancer SNAC (sodium N-[8-(2-hydroxybenzoyl)amino] caprylate), which causes a localized increase in pH. This enables higher solubility and protects from enzymatic degradation. The patients in the phase 2 study experienced dose-dependent decreases in their HbA_{1c} and had similar results in their weight loss and other secondary outcomes.[69] Mild-to-moderate GI side effects were the most frequently reported adverse events, which included nausea (13%-34%), vomiting (6%-22%), and diarrhea (7%-23%).[69]

Comparison of GLP-1 Receptor Agonists

Currently, 5 GLP-1 receptor agonists are FDA-approved in the United States for the treatment of patients with type 2 diabetes. Their formulations vary from the twice-daily injection of exenatide to once-weekly formulations of albiglutide, exenatide ER, and dulaglutide. Several head-to-head comparison studies have compared the GLP receptor agonists. A new drug is currently under FDA review.

Comparing exenatide twice daily with exenatide once weekly showed a significantly greater reduction of HbA_{1c} with exenatide ER (difference, 0.7%)[17]; the adverse effects were similar, but injection-site reactions were more common with exenatide ER. In DURATION-6, once-daily treatment with liraglutide 1.8 mg resulted in significantly greater reduction of HbA_{1c} (difference, 0.21%) and greater weight loss (difference, 0.90 kg) in comparison with once-weekly exenatide 2 mg, although GI adverse events occurred more often with patients taking liraglutide.[22]

Similarly, in LEAD-6, liraglutide 1.8 mg had a significantly greater HbA_{1c} reduction (difference, –0.33%) and less adverse effects, including hypoglycemia, than exenatide 10 mcg twice daily.[33] HARMONY-7 compared once-weekly albiglutide 50 mg with liraglutide 1.8 mg and showed greater HbA_{1c} reduction with liraglutide (difference, 0.21%; noninferior).[45] There were more injection-site reactions with albiglutide (difference, 7.5%), but more GI events with liraglutide (difference, 13.1%).[45] AWARD-6 compared once-weekly dulaglutide 1.5 mg with liraglutide 1.8 mg, showing greater HbA_{1c} reduction with dulaglutide (difference, –0.06%; noninferior), although liraglutide had significantly greater weight loss (difference, 0.71 kg). No significant differences in the adverse-effect profile were noted in the study.[53]

GETGOAL-X compared lixisenatide 20 mcg with exenatide 10 mcg twice daily and showed similar HbA_{1c} reduction, although there was less hypoglycemia and nausea with lixisenatide.[63] Lixisenatide is currently marketed mainly as a 5-mcg dose in combination with insulin glargine (Soliqua).

Conclusion

The GLP-1 receptor agonists are valuable options for the treatment of type 2 diabetes as adjunctive therapy or as monotherapy. There is robust evidence supporting the indication for the use of GLP-1 receptor agonists if patients are overweight or obese, have CV disease or renal disease, or are at high risk for hypoglycemia—common comorbidities of type 2 diabetes. Clinical trials demonstrate the superiority of GLP-1 receptor agonists to other antidiabetes drugs in HbA_{1c} reduction, blood pressure reduction, and weight loss, without hypoglycemia risk. Unlike metformin, there is no contraindication to giving patients with renal disease a GLP-1 receptor agonist. Although some significant differences exist among the agents in this class, the efficacy of the individual agents is generally comparable. Choosing among the available GLP-1 receptor agonists will likely depend on patient preferences, reaction to adverse effects, and cost. ■

Author Disclosure Statement

Dr Tran, Dr Park, Dr Pandya, Dr Muliyil, Dr Jensen, and Dr Huynh reported no conflicts of interest. Dr Nguyen is on the Speaker's Bureau for AstraZeneca, Janssen, and sanofi-aventis.

References

1. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf. Accessed May 9, 2017.

2. American Diabetes Association. Standards of Medical Care in Diabetes—2017. *Diabetes Care*. 2017;40(suppl 1):S1-S135.

3. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care*. 2013;36:1033-1046.

Continued

4. Byrne MM, Sturis J, Sobel RJ, Polonsky KS. Elevated plasma glucose 2 h postchallenge predicts defects in beta-cell function. *Am J Physiol*. 1996;270(4 pt 1):E572-E579.
5. Bergstrom RW, Wahl PW, Leonetti DL, Fujimoto WY. Association of fasting glucose levels with a delayed secretion of insulin after oral glucose in subjects with glucose intolerance. *J Clin Endocrinol Metab*. 1990;71:1447-1453.
6. Steiner KE, Mouton SM, Bowles CR, et al. The relative importance of first- and second-phase insulin secretion in countering the action of glucagon on glucose turnover in the conscious dog. *Diabetes*. 1982;31:964-972.
7. Mitrakou A, Kelley D, Mokan M, et al. Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med*. 1992;326:22-29.
8. Bruttomesso D, Pianta A, Mari A, et al. Restoration of early rise in plasma insulin levels improves the glucose tolerance of type 2 diabetic patients. *Diabetes*. 1999;48:99-105.
9. Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1986;29:46-52.
10. Vilsbøll T, Krarup T, Madsbad S, Holst JJ. Defective amplification of the late phase insulin response to glucose by GIP in obese type II diabetic patients. *Diabetologia*. 2002;45:1111-1119.
11. Vilsbøll T, Agersø H, Krarup T, Holst JJ. Similar elimination rates of glucagon-like peptide-1 in obese type 2 diabetic patients and healthy subjects. *J Clin Endocrinol Metab*. 2003;88:220-224.
12. Coleman CI, Gryskiewicz KA. Exenatide: a novel incretin mimetic hormone for the treatment of type 2 diabetes. *Formulary*. 2005;40:86-90.
13. Jose B, Tahrani AA, Piya MK, Barnett AH. Exenatide once weekly: clinical outcomes and patient satisfaction. *Patient Prefer Adherence*. 2010;4:313-324.
14. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med*. 2011;154:103-112.
15. Bydureon (exenatide extended-release) for injectable suspension [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; September 2015.
16. Buse JB, Drucker DJ, Taylor KL, et al; for the DURATION-1 Study Group. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care*. 2010;33:1255-1261.
17. Drucker DJ, Buse JB, Taylor K, et al; for the DURATION-1 Study Group. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372:1240-1250.
18. Wysham C, Bergenstal R, Malloy J, et al. DURATION-2: efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide. *Diabet Med*. 2011;28:705-714.
19. Diamant M, Van Gaal L, Guerci B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. *Lancet Diabetes Endocrinol*. 2014;2:464-473. Erratum in: *Lancet Diabetes Endocrinol*. 2014;2:e13.
20. Russell-Jones D, Cuddihy RM, Hanefeld M, et al; for the DURATION-4 Study Group. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naïve patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. *Diabetes Care*. 2012;35:252-258.
21. Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011; 96:1301-1310.
22. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013;381:117-124.
23. Harder H, Nielsen L, Tu DT, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. *Diabetes Care*. 2004;27:1915-1921.
24. Rolin B, Larsen MO, Gotfredsen CF, et al. The long-acting GLP-1 derivative NN2211 ameliorates glycemia and increases beta-cell mass in diabetic mice. *Am J Physiol Endocrinol Metab*. 2002;283:E745-E752.
25. Larsen PJ, Fledelius C, Knudsen LB, Tang-Christensen M. Systemic administration of the long-acting GLP-1 derivative NN2211 induces lasting and reversible weight loss in both normal and obese rats. *Diabetes*. 2001;50:2530-2539.
26. Gerich JE. Is reduced first-phase insulin release the earliest detectable abnormality in individuals destined to develop type 2 diabetes? *Diabetes*. 2002; 51(suppl 1):S117-S121.
27. Vilsbøll T, Brock B, Perrild H, et al. Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with type 2 diabetes mellitus. *Diabet Med*. 2008;25:152-156.
28. Marre M, Shaw J, Brändle M, et al; for the LEAD-1 SU Study Group. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med*. 2009;26:268-278.
29. Nauck M, Frid A, Hermansen K, et al; for the LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (Liraglutide Effect and Action in Diabetes)-2 Study. *Diabetes Care*. 2009;32:84-90.
30. Garber A, Henry R, Ratner R, et al; for the LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet*. 2009;373:473-481.
31. Zinman B, Gerich J, Buse JB, et al; for the LEAD-4 Study Investigators. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care*. 2009;32:1224-1230. Erratum in: *Diabetes Care*. 2010;33:692.
32. Russell-Jones D, Vaag A, Schmitz O, et al; for the Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia*. 2009;52:2046-2055.
33. Buse JB, Rosenstock J, Sesti G, et al; for the LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374:39-47.
34. Pratley RE, Gilbert M. Targeting incretins in type 2 diabetes: role of GLP-1 receptor agonists and DPP-4 inhibitors. *Rev Diabet Stud*. 2008;5:73-94.
35. DeFronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2005;28:1092-1100.
36. Montanya E, Sesti G. A review of efficacy and safety data regarding the use of liraglutide, a once-daily human glucagon-like peptide 1 analogue, in the treatment of type 2 diabetes mellitus. *Clin Ther*. 2009;31:2472-2488.
37. Thompson PL, Davis TM. Cardiovascular effects of glucose-lowering therapies for type 2 diabetes: new drugs in perspective. *Clin Ther*. 2017;39:1012-1025.
38. Tanzeum (albiglutide) for injection [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; September 2016.
39. Reusch J, Stewart MW, Perkins CM, et al. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. *Diabetes Obes Metab*. 2014;16:1257-1264.
40. Nauck MA, Stewart MW, Perkins C, et al. Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (HARMONY 2): 52 week primary endpoint results from a randomised, placebo-controlled trial in patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetologia*. 2016;59:266-274.
41. Ahrén B, Johnson SL, Stewart M, et al; for the HARMONY 3 Study Group. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care*. 2014;37:2141-2148.
42. Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. *Diabetologia*. 2014;57:2475-2484.
43. Home PD, Shamanna P, Stewart M, et al. Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. *Diabetes Obes Metab*. 2015;17:179-187.
44. Rosenstock J, Fonseca VA, Gross JL, et al; for the HARMONY 6 Study Group. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care*. 2014;37:2317-2325.
45. Pratley RE, Nauck MA, Barnett AH, et al; for the HARMONY 7 Study Group. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol*. 2014;2:289-297. Erratum in: *Lancet Diabetes Endocrinol*. 2014;2:e5.
46. Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study. *Diabetes Care*. 2014;37:2723-2730.

47. Trulicity (dulaglutide) injection [prescribing information]. Indianapolis, IN: Eli Lilly; February 2017.
48. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care*. 2014;37:2159-2167. Errata in: *Diabetes Care*. 2014;37:2895; *Diabetes Care*. 2015;38:1393-1394.
49. Giorgino F, Benroubi M, Sun JH, et al. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). *Diabetes Care*. 2015;38:2241-2249.
50. Umpierrez G, Tofé Povedano S, Pérez Manghi F, et al. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). *Diabetes Care*. 2014;37:2168-2176.
51. Blonde L, Jendle J, Gross J, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. *Lancet*. 2015;385:2057-2066.
52. Nauck M, Weinstock RS, Umpierrez GE, et al. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care*. 2014;37:2149-2158. Erratum in: *Diabetes Care*. 2015;38:538.
53. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384:1349-1357. Erratum in: *Lancet*. 2014;384:1348.
54. Dungan KM, Weitgasser R, Perez Manghi F, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). *Diabetes Obes Metab*. 2016;18:475-482.
55. Adlyxin (lixisenatide) injection [prescribing information]. Bridgewater, NJ: sanofi-aventis US; July 2016.
56. Seino Y, Yabe D, Takami A, et al. Long-term safety of once-daily lixisenatide in Japanese patients with type 2 diabetes mellitus: GetGoal-Mono-Japan. *J Diabetes Complications*. 2015;29:1304-1309.
57. Fonseca VA, Alvarado-Ruiz R, Raccah D, et al; for the EFC6018 GetGoal-Mono Study Investigators. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). *Diabetes Care*. 2012;35:1225-1231.
58. Bolli GB, Munteanu M, Dotsenko S, et al. Efficacy and safety of lixisenatide once daily vs. placebo in people with type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). *Diabet Med*. 2014;31:176-184.
59. Onishi Y, Niemoeller E, Ikeda Y, et al. Efficacy and safety of lixisenatide in Japanese patients with type 2 diabetes mellitus inadequately controlled by sulfonylurea with or without metformin: subanalysis of GetGoal-S. *J Diabetes Investig*. 2015;6:201-209.
60. Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). *Diabetes Care*. 2013;36:2489-2496.
61. Pinget M, Goldenberg R, Niemoeller E, et al. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). *Diabetes Obes Metab*. 2013;15:1000-1007.
62. Seino Y, Min KW, Niemoeller E, Takami A; for the EFC10887 GETGOAL-L Asia Study Investigators. Randomized, double-blind, placebo-controlled trial of the once-daily glp-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). *Diabetes Obes Metab*. 2012;14:910-917.
63. Rosenstock J, Raccah D, Korányi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care*. 2013;36:2945-2951.
64. Yu Pan C, Han P, Liu X, et al. Lixisenatide treatment improves glycaemic control in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin with or without sulfonylurea: a randomized, double-blind, placebo-controlled, 24-week trial (GetGoal-M-Asia). *Diabetes Metab Res Rev*. 2014;30:726-735.
65. Pfeffer MA, Claggett B, Diaz R, et al; for the ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373:2247-2257.
66. Novo Nordisk. Novo Nordisk files for regulatory approval of once-weekly semaglutide with the FDA for the treatment of type 2 diabetes. Press release. December 5, 2016. http://press.novonordisk-us.com/2016-12-05-Novo-Nordisk-Files-for-Regulatory-Approval-of-Once-Weekly-Semaglutide-with-the-FDA-for-the-Treatment-of-Type-2-Diabetes. Accessed May 18, 2017.
67. Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem*. 2015;58:7370-7380.
68. Marso SP, Bain SC, Consoli A, et al; for the SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834-1844.
69. Jabbour S, Pieber TR, Rosenstock J, et al. Robust dose-dependent glucose lowering and body weight (BW) reductions with the novel oral formulation of semaglutide in patients with early type 2 diabetes (T2D). *Endocr Rev*. 2016; 37(2 suppl):Abstract OR15-3.

STAKEHOLDER PERSPECTIVE

The GLP-1 Receptor Agonists Are Cost-Effective for the Treatment of Type 2 Diabetes

By Raymond Plodkowski, MD

Endocrinology and Metabolism Division, Scripps Clinic, San Diego, CA, and Associate Clinical Professor of Medicine, University of California, San Diego

PATIENTS: In the past 2 decades, the care of patients with type 2 diabetes has evolved. With therapeutic advances and falling glycated hemoglobin (HbA_{1c}) levels, the prevalence of catastrophic complications has slowly declined. Data from the Centers for Disease Control and Prevention show that the rates of lower-limb amputations, end-stage kidney failure, and deaths resulting from high blood glucose (ie, hyperglycemia) have all declined.[1] However, as the article by Tran and colleagues points out, some of the older classes of diabetes medications used to lower HbA_{1c}, such as sulfonylureas or insulin, are often associated with an increased risk for other complications, such as hypoglycemia and weight gain.[2]

Newer glucagon-like peptide (GLP)-1 receptor agonists have the ability to control glucose while reducing hypoglycemia, as well as promoting weight reduction.

STAKEHOLDER PERSPECTIVE *Continued*

Weight reduction is key to breaking the cycle of patients sequentially adding medications to treat type 2 diabetes. For example, a 3-year study compared the once-weekly GLP-1 analog exenatide extended release with titrated insulin glargine.[3] In addition to superior HbA_{1c} control at 3 years, exenatide had a 3-fold reduction of hypoglycemia per patient annually; and at the end of the 3-year study period, the insulin group gained 4.4 pounds and the exenatide group lost 5.5 lbs.[3] Thus, patients had improved glycemic control, less hypoglycemia, and weight reduction, using 1 injection weekly rather than daily insulin injections. These are all positive benefits to patients.

PAYERS: Type 2 diabetes is a very cost-intensive disease to manage. A study that examined insurance claims data showed that the cumulative 1-year and 3-year costs for adults who were currently receiving antidiabetes drug therapy were $23,322 and $74,862, respectively.[4]

The high cost of diabetes is often driven by 3 factors. First is the addition of costly medications after other therapies fail and glycemic control deteriorates. Progression to insulin therapy is especially costly, because in addition to the cost of insulin, payers must provide ancillary supplies, such as insulin pen needles or syringes; patients who require insulin therapy also typically have a higher utilization of test strips. Second, there are costs associated with hypoglycemia, and the third are associated complications, such as retinopathy, neuropathy, amputations, and diabetes-related renal disease. Although the rates of complications have improved, they are still problematic. GLP-1 drugs have the potential to improve all 3 of these areas of concern.

HbA_{1c} is the standard for measuring glycemic control; however, this measure reflects a 3-month average and does not capture hyperglycemia and hypoglycemia, which are key to understanding the morbidity associated with diabetes. It has been shown that a patient with diabetes spends approximately 67% of time in a euglycemia range (70-180 mg/dL), 29% of time in the hyperglycemia range (>180 mg/dL), and 4% in the hypoglycemia range (<70 mg/dL).[5]

Hypoglycemia is a major driver of total costs for patients with type 2 diabetes; a 59.4% increase in total 1-year costs was seen for patients who had a hospitalization or emergency department visit for a hypoglycemic event.[4] Another study determined that hypoglycemic episodes requiring assistance from a healthcare providers cost an average of $1161.[6] GLP-1 drugs offer a mechanism of action of improved glycemic levels and a minimal risk for hypoglycemia, which has the potential for cost-savings while reducing this costly complication. The GLP-1 liraglutide was shown to cause durable HbA_{1c} control, with less hypoglycemia and with weight reduction versus insulin glargine.[7]

Cardiovascular (CV) complications are also costly. In a large randomized, prospective study of 9340 patients, with a median follow-up of 3.8 years, fewer patients died from CV causes in the liraglutide group, with a 22% reduction in CV death, compared with patients receiving placebo (4.7% vs 6.0%, respectively; $P = .007$).[8] In addition, a 13% reduction was seen in the combined major adverse cardiac events of CV-related death, nonfatal myocardial infarction, and nonfatal stroke ($P = .01$).[8]

So although GLP-1 drugs have their own costs, their benefits are many, including superior HbA_{1c} control, reduced hypoglycemia, and weight reduction—all of which can help to lower the overall cost of care. ■

1. Centers for Disease Control and Prevention. New CDC data show declines in some diabetes-related complications among US adults. April 16, 2014. www.cdc.gov/media/releases/2014/p0416-diabetes-complications.html. Accessed June 8, 2017.
2. Tran KL, Park YI, Pandya S, et al. Overview of glucagon-like peptide-1 receptor agonists for the treatment of patients with type 2 diabetes. *Am Health Drug Benefits*. 2017;10(4):178-188.
3. Diamant M, Van Gaal L, Guerci B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. *Lancet Diabetes Endocrinol*. 2014;2:464-473. Erratum in: *Lancet Diabetes Endocrinol*. 2014;2:e13.
4. Meng J, Casciano R, Lee YC, et al. Effect of diabetes treatment-related attributes on costs to type 2 diabetes patients in a real-world population. *J Manag Care Spec Pharm*. 2017;23:446-452.
5. Bode BW, Schwartz S, Stubb HA, Block JE. Glycemic characteristics in continuously monitored patients with type 1 and type 2 diabetes: normative values. *Diabetes Care*. 2005;10:2361-2366.
6. Foos V, Varol N, Curtis BH, et al. Economic impact of severe and non-severe hypoglycemia in patients with type 1 and type 2 diabetes in the United States. *J Med Econ*. 2015;18:420-432.
7. Russell-Jones D, Vaag A, Schmitz O, et al; for the Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia*. 2009;52:2046-2055.
8. Marso SP, Daniels GH, Brown-Frandsen K, et al; for the LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-322.